REMARKS

Status of Claims

Claim 1 is the only claim pending in the application. Claim 1 is rejected.

Claim of Priority

The Examiner has acknowledged Applicant's claim to priority to Japanese Application No. 2002-249821 filed August 29, 2002, and receipt of "some" of the priority documents.

Since Applicant claims priority to only one application, and PAIR indicates that JP 2002-249821 was received February 25, 2005, Applicants respectfully request acknowledgement of receipt of all the priority documents.

Information Disclosure Statements

Applicants thank the Examiner for the acknowledgment of the Information Disclosure Statements filed February 25, 2005, and August 10, 2005, by returning initialed copies of the PTO Form SB/08. Applicants note that no PTO Forms SB/08 are outstanding.

Rejection under § 103(a)

Claim 1 is rejected under 35 U.S.C. § 103(a) as being obvious over EP 1 333 025 A1 to Fukushima (WO 02/038541; hereinafter "Fukushima") in view of Berge et al. (Journal of Pharmaceutical Sciences, Vol. 66 pp. 1-19 (1977); hereinafter "Berge").

The Examiner asserts that the instant invention is drawn to a benzenesulfonate salt of (2S, 4S)-2-cyano-4-fluoro-1-[(2-hydroxy-1,1-dimethyl)ethlylamino]acetylpyrrolidine, which is allegedly a dipeptidyl peptidase IV (DPPIV) inhibitor.

The Examiner asserts that the cyanopyrrolidine derivative of Formula (I) disclosed in Fukushima is allegedly comparable to the present invention when R1 is fluoro, R^2-R^4 is hydrogen, X is oxygen, Y is CR^5R^6 wherein R^5R^6 represent hydrogen, and Z represents (2-hydroxy-1,1-dimethyl)ethyl. The Examiner asserts that the claimed invention is a species of a subgenus.

The Examiner also asserts that one of ordinary skill in the art would have the motivation to make and use the claimed invention from the cited documents because allegedly structurally similar chemical compounds are expected to have generally similar properties and utilities. In particular, the Examiner asserts that the expectation of success is derived from the preferred embodiments and preferred subgenus of the cited documents. The Examiner points to Formula 2 on pages 4-5 of Fukushima for this proposition, and asserts that Fukushima teaches how to make the claimed compounds and disclose a protocol used to test the compounds for the inhibitory effects.

With regard to Berge, the Examiner asserts that the claimed benezenesulfonate salt form is disclosed in Berge as a commercially marketed salt, and Berge discloses that pharmaceutical agents may be manipulated and optimized by salt forms.

Applicants note that Fukushima is directed to cyanopyrrolidine derivatives represented by Formula (1). As discussed at page 1, lines 15-22 of the present specification, although the compound disclosed in Fukushima is a dipeptidyl peptidase IV inhibitor (DPPIV), the compound has a low solid-state stability in free form, and the mineral or organic salts disclosed are disadvantageous as having for instance, low solid-state stability, low stability under humidified conditions, and synthesis difficulty. As admitted by the Examiner, Fukushima does not teach the claimed benzenesulfonate salt of the claimed compound. Instead, Fukushima is drawn to any pharmaceutical salt form.

There is no direction or guidance in Fukushima to provide one of ordinary skill in the art with a reason to pick the benzenesulfonate salt from amongst the extensive list of pharmaceutical salts disclosed in Berge and combine it with the cyanopyrrolidine compound of Fukushima to obtain the claimed compound. Applicants note that Berge is a general review article surveying the literature to compare the properties of different salt forms of the same compound for the purpose of presenting an overview of the different salts from which new drug candidates may be chosen and to assemble data to provide for a rational basis for selecting a suitable salt form (page 1, column 2, 3rd paragraph of Berge). Benzenesulfonate is disclosed in Table 1 of Berge as a FDA-approved commercially marketed salt.

Applicants remind the Office Action that if there is nothing to indicate a chemical compound would have unique and unexpected properties, it would not be obvious to make it.[1] Applicants note that Berge is a general review article that does not single out the benzenesulfonate salt as an advantageous pharmaceutical salt imparting e.g., increased stability, to a cyanopyrrolidine compound. Also, Berge discloses that "[v]arious salts of the same compound behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound" (page 2, column 1, 2nd paragraph of Berge) so that it would not have been obvious to one of ordinary skill in the art, absent an explicit reason to pick the benzenesulfonate salt from amongst the extensive list of pharmaceutical salts disclosed in Berge and combine it with the cyanopyrrolidine compound of Fukushima, to obtain the claimed compound.

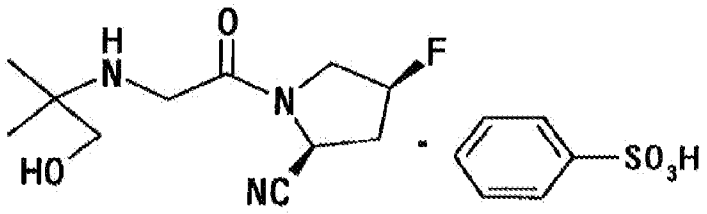
Furthermore, Applicants note that Tables 1-3 at pages 8-9 and 11 of the present specification and the Declaration Under 37 C.F.R. §1.132 (hereinafter "Declaration") submitted herewith show the unexpected superior properties of the claimed compound in comparison to other salts.

In particular, Applicants submit that the claimed composition has unexpected effects over Fukushima in view of Berge as explained below, and thus, is patentable.

Features of the present invention

The present invention relates to a "benzenesulfonate salt of (2S,4S)-2-cyano-4-fluoro-l-[(2-hydroxy-1,1-dimethyl)-ethylamino]acetylpyrrolidine" (see Claim 1) (hereinafter referred to as "the subject compound").

[1] In re Lindell, 385 F.2d 453 (CCPA 1967).



The crystallinity and physical properties such as storage stability, formulation properties and solubility, of the subject compound are discussed below.

(A) Crystallinity

Most pharmaceutical preparations, including the subject compound, are prepared in the form of a crystalline powder. Pharmaceutical preparations are strongly required not only to have constant high quality so that their efficacy is developed as expected, but also to ensure their safety. In terms of ensuring the quality of pharmaceutical preparations, it is particularly important to provide active ingredients with high purity and in a uniform crystal form, i.e., active ingredients having a good crystallinity. When crystallinity is either poor or too good, impurities are likely to be incorporated and it is therefore difficult to obtain crystals with high purity. Moreover, when there is crystal polymorphism, transfer may occur between crystals and may constitute a problem in providing products of constant quality because there are differences in properties (e.g., solid-state stability and solubility) among individual crystal forms. In the case of a hydrate-forming compound or salt, subtle changes in crystallization conditions may result in different crystal forms (anhydrides or hydrates with different numbers of water molecules). Moreover, there is also a fear that some drying conditions may induce dehydration and may cause conversion into a different crystal form. Thus , it is not easy to achieve constant production of hydrates in a uniform crystal form. Further, to provide pharmaceutical

preparations with stable quality at an industrial scale, there is a need for easy handling, such as to enable easy collection of crystals with high purity and in high yield.

When compounds are formed in the salt form, differences in their structure will produce a wide variety of influences on their crystallinity (e.g., presence or absence of polymorphism) and such influences are impossible to expect. It is therefore difficult to find a salt having the above crystallinity required for pharmaceutical preparations.

In spite of these difficult circumstances, the benzenesulfonate salt of the present invention has an advantageous effect in that it is particularly excellent in the crystallinity required for pharmaceutical preparations, as explained above, when compared to other salts.

To further prove the above effect, the experimental data on comparison of crystallinity between the benzenesulfonate salt of the present invention and the corresponding tosylate salt is submitted in the attached Declaration.

The reason why the tosylate salt was selected as a control for comparison purposes is because a tosylate salt is structurally most similar to and also more commonly used as a pharmaceutical preparation than a benzenesulfonate salt.

In the attached Declaration, standard crystallization procedures were used to study the easiness of salt preparation. Likewise, thermal analysis and powder X-ray diffractometry were used to study the presence or absence of crystal polymorphism.

As a result, the tosylate salt had too good a crystallinity and started to crystallize before the free form was completely dissolved, so that it was crystallized in a state incorporating impurities including the free form. Thus, due to having too good a crystallinity, the tosylate salt was likely to incorporate impurities and was difficult to obtain as a crystal of high purity.

In contrast, in the case of the benzenesulfonate salt of the present invention, when a solution of benzenesulfonic acid in methanol was added dropwise to a suspension of the free form in methanol, the free form was rapidly dissolved and a solid crystal was then precipitated, thus obtaining the subject compound of high purity without contamination with the free form. Moreover, since the generated crystal was of an appropriate size, the crystal showed a good filtration property during its collection by filtration and hence was excellent in handling. These results indicate that because of its good crystallinity, the benzenesulfonate salt of the present invention is easy to collect as a crystal of high purity and also easy to handle as a crystal.

Further, upon thermal analysis using the crystals obtained through the above standard crystallization procedures (i.e., crystallization from methanol-isopropyl ether), the results suggested the presence of polymorphism for the tosylate salt, but gave no indication of polymorphism for the claimed benzenesulfonate salt of the present invention (see Figures 1 and 2 in the attached Declaration). Polymorphism was further studied by thermal analysis and powder X-ray diffractometry for the claimed benzenesulfonate salt of the present invention when crystallized from other solvent systems. As a result, even when crystallized from other solvent systems, the claimed benzenesulfonate salt of the present invention produced exactly the same results as when it was crystallized from methanol-isopropyl ether (see Figures 1 and 3 in the attached Declaration). The results gave no indication of polymorphism with the claimed benzenesulfonate salt of the present invention.

Likewise, when the claimed benzenesulfonate salt of the present invention was also studied for the presence or absence of hydrates, the results gave no indication of hydrate generation even in the case of recrystallization from hydrous ethanol.

Applicants note that the claimed benzenesulfonate salt of the present invention was obtained in an extremely high yield of 98% from the above standard crystallization procedures.

In view of the foregoing, the benzenesulfonate salt of the present invention has no polymorphism nor hydrates, has a good crystallinity its crystal structure has highly pure and uniform crystal form, and has excellent handling to provide easy collection of its crystal form with high purity and in high yield. Thus, the claimed benzenesulfonate salt of the present invention provides a pharmaceutical preparation with stable quality at an industrial scale.

(B) Physical properties

When compounds are formed in salt form, it is known that their physical properties (e.g., solubility, storage stability (including moisture resistance), formulation properties) are influenced. However, such an influence cannot be absolutely predicted because it will greatly vary depending on differences in the compound structure. In pharmaceutical preparations, the solubility of active ingredients is most particularly important in showing their efficacy because it will influence the biological effectiveness of the pharmaceutical preparations. However, improved moisture resistance will usually lead to reduced solubility , so that active ingredients will often become difficult to dissolve. Thus, in general, it is often difficult to improve storage stability including moisture resistance, without excessive reduction of solubility.

However, as discussed below, the claimed benzenesulfonate salt of the present invention not only solves the problem of storage stability (including hygroscopicity) found in the corresponding hydrochloride salt conventionally used, but also has an advantageous effect in that it is resistant to moisture, is very stable either under heated conditions or heated and humidified conditions, is excellent in formulation properties, and maintains its solubility at a high level .

(1) Storage stability (including moisture resistance), formulation properties

(a) The claimed benzenesulfonate salt of the present invention showed no change in its weight and no deliquescence even when stored at room temperature under humidified conditions for 3 days. In contrast, the corresponding hydrochloride and methanesulfonate salts both absorbed moisture and thus deliquesced (see Test Example 1 in the specification of the present application).

(b) When stored under heated and humidified conditions (40°C, 75% RH) for one month or under heated conditions (70°C) for 3 days, the benzenesulfonate salt of the present invention showed a remaining percentage of 99% or more under either condition. In contrast, the hydrochloride and methanesulfonate salts both showed a remaining percentage of 97% or less under either condition (see Test Example 2 in the specification of the present application).

(c) After storage at 65°C for one week, the claimed benzenesulfonate salt of the present invention showed a remaining percentage of 99.1% in Recipe A (10 mg drug substance, 68 mg crystalline cellulose, 2 mg magnesium stearate) and a remaining percentage of 91.6% in Recipe B which included 16 μl purified water for humidification (10 mg drug substance, 68 mg lactose, 2 mg hydrogenated oil). Thus, the claimed benzenesulfonate salt of the present invention showed little change in its compatibility with additives. In contrast, the methanesulfonate salt showed a remaining percentage of 91.6% in Recipe A and 74.5% in Recipe B (see Test Example 3 in the specification of the present application).

(2) Solubility

The subject compound has a solubility of 76.4 mg/mL (25°C in water) . The subject compound not only has very high storage stability (including moisture resistance), as explained

above, but also maintains high solubility because the claimed compound exhibits no loss in its solubility naturally required to show its efficacy as a drug. This is a remarkably advantageous effect which one of ordinary skill in the art cannot expected because it is commonly known in the art that improved moisture resistance will usually lead to reduced solubility, often making dissolution difficult.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejections under §103(a).

CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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